DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

M3652N

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

APR 14 2000

WARNING LETTER
Via Federal Express

Bruce DeWoolfson, Ph.D.
President
Euclid Systems Corporation
2810 Towerview Road
Herndon, Virginia 20171

Dear Dr. DeWoolfson:

The purpose of this Warning Letter is to inform you of objectionable conditions found during a Food and Drug Administration (FDA) inspection of your site, to discuss your written response to the deviations noted, and to request a prompt reply with regard to the remaining issues. The inspection took place during the period of January 18 and February 16, 2000, and was conducted by Ms. Christine M. Whitby, Mr. Steven J. Thurber, and Ms. Candice J. Cortes, investigators from FDA's Baltimore District Office. Also present during the inspection were Mr. Alan C. Gion from the Baltimore District Office and Ms. Eleanor Felton from the Office of Device Evaluation (ODE), Center for Devices and Radiological Health (CDRH). The purpose of the inspection was to determine if your activities as sponsor of clinical studies of [redacted] comply with applicable FDA regulations. These [redacted] are devices as that term is defined in Section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act).

The inspection was conducted under a program designed to ensure that data and information contained in requests for Investigational Device Exemptions (IDE), Premarket Approval Applications (PMA), and Premarket Notifications [510(k)] are scientifically valid and accurate. Another objective of the program is to ensure that human subjects are protected from undue hazard or risk during the course of scientific investigations.

Our review of the inspection report submitted by the district office revealed serious violations of requirements of Title 21, Code of Federal Regulations (21 CFR), Part 812 - Investigational Device Exemptions, Part 50 - Protection of Human Subjects, and Section 520(g) of the Act. You received a form FDA-483, "Inspectional Observations," at the conclusion of the inspection that listed the deviations noted and discussed with you. We acknowledge receipt of a copy of your response, dated March 1, 2000, received at your March 2 meeting with CDRH. The deviations noted on the form FDA-483, our subsequent review of the inspection report, and your response to the FDA-483 items are discussed below. Deviations noted include:

Failure to properly monitor the clinical study (21 CFR 812.46).
21 CFR 812.46 requires sponsors to secure compliance of all investigators and to assure that adverse effects are adequately reviewed and the findings shared with all investigators. There is no documentation that action was taken to correct deviations from protocol by investigators or that investigators were warned that they would be discontinued from the study if they did not comply with the protocol. Numerous case report forms (CRFs) have not been submitted as required. Moreover, proper consent procedures are not being followed; informed consent documents were obtained after the initial study visit and, in several cases, were missing altogether. There is also no documentation that all investigators were notified when adverse reactions occurred. While adverse reactions were recorded on CRFs, they were not reported to the sponsor and IRB as required in the protocol.

Failure to have written monitoring procedures [21 CFR 812.25(e)].
No standard operation procedures (SOPs) for monitoring clinical studies exists--only monitoring procedures submitted as part of the investigational plan in the Investigational Device Exemption (IDE) application for this study. No copy of the IDE was available.

Failure to obtain signed investigator agreements from all clinical investigators [21 CFR 812.43(c)].
No signed investigator agreements were found for 4 of the 15 investigators/sub-investigators participating in the study.

Commercialization of an investigational device [21 CFR 812.7(b)].
A sponsor cannot charge a subject a price larger than that necessary to recover costs of manufacture, research, development, and handling. Up to $100.00 per pair was charged for [redacted] supplied to individuals outside of the study; study subjects paid a deposit fee of $40.00 a pair. An FDA Public Health Notification dated September 25, 1998 (copy enclosed) states that a licensed practitioner may individually design and prescribe an [redacted] for a particular patient within the scope of his/her practice. Your firm shipped 920 investigational [redacted] within the United States outside of the study. Moreover, 13,101 were exported to Asia; and 153 were exported to Canada. No export permit for these [redacted] had been obtained from FDA.

Failure to maintain accurate and complete accountability records [21 CFR 812.140(b)(2)].
There is no log of [redacted] returned. Dr. [redacted] reordered 21 [redacted] as a result of a variety of problems but no listing of those returned, or the reasons for their return, was maintained. Moreover, all [redacted] are to be returned by the study subjects at the completion of the study. The study duration is 9 months. No record of [redacted] returned as a result of study completion is maintained.

Failure to document institutional review board (IRB) approval (21 CFR 812.40). Sponsors are responsible for ensuring that IRB review and approval are obtained.

The deviations listed above are not intended to be an all-inclusive list of deficiencies that may exist in your clinical study. It is your responsibility as a sponsor to ensure that the investigation is conducted in accordance with applicable FDA regulations.

We are aware that Euclid has hired a new study monitor, [redacted]. He was present at the March 2 meeting with CDRH. Your written response states that measures are in place to insure that monitoring deficiencies do not occur in the future. Written procedures for the monitoring process adopted need to be developed if they do not presently exist. Please send a copy of these procedures to the Division of Bioresearch Monitoring (DBM) at the address below.

According to your response, as CRFs are completed, they will be sent to the study monitor via a toll-free facsimile line. The monitor will review these in a timely way and report monthly to Euclid Quality Assurance as to the progress of the study. The telephone log will be maintained as evidence of data transmitted. Moreover, a monitor 800 number has been sent to all participating investigators and a telephone log of all incoming and outgoing contacts with investigators and regulatory bodies will be maintained.

Moreover, your response states that no new subjects will be entered into the study before the informed consent, initial examination report form, and lens order is sent by facsimile to the study monitor. The monitor will need to assure Euclid Manufacturing in writing that the informed consent has been properly executed before lenses are shipped.

Your response states, and Mr. [redacted] reiterated at the meeting (meeting minutes enclosed), that site audits of all study investigators are in progress. These include assessment of the site facilities and, when necessary, instructions on the protocol and investigational plan. As requested at the March 2 meeting, [redacted] submitted a copy of their auditing procedures to Carl DeMarco, Integrity Officer, Office of Device Evaluation (ODE) for review. Please submit to DBM a schedule of the site audits completed, in progress, and yet to be accomplished.

You state that you are in the process of accumulating signed investigator agreements and curriculum vitae for all 15 investigators/sub-investigators participating in the study. Moreover, through the site audit visits you are accumulating an accurate file of IRB approvals and correspondence. Please submit to DBM a copy of all signed investigator agreements and documentation of IRB approvals, including the most recent continuing review approval.

Regarding [redacted] retained by study subjects, you have chosen to supplement your protocol to allow satisfied subjects to keep thei[redacted] provided they agree to

return for periodic follow-up. Please advise us as to the status of your IDE supplement and include a copy of the revisions to your protocol.

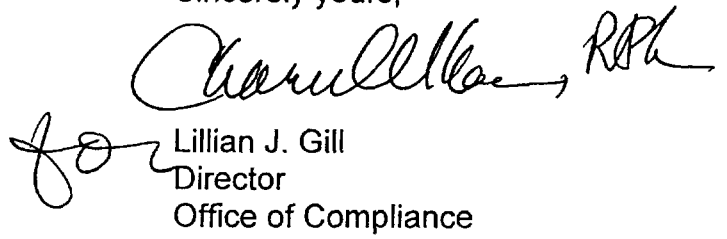
With regard to the issue of commercialization, you state that you have sent a notification to all of your customers and are applying for an export license. Please submit a copy of the original notification, including the attached seminar information, as well as an update as to the status of your export license.

Please send the information requested above, within 15 working days of receipt of this letter, to the Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Program Enforcement Branch II (HFZ-312), 2098 Gaither Road, Rockville, Maryland 20850, Attention: Jean Toth-Allen, Ph.D. Failure to respond could result in further regulatory action, such as civil money penalties, without additional notice.

A copy of this letter has been sent to FDA's Baltimore District Office, 900 Madison Avenue, Baltimore, Maryland 21201. We request that a copy of your response also be sent to that office.

If you have any questions, feel free to contact Jean Toth-Allen, Ph.D. at (301) 594-4723, ext. 141.

Sincerely yours,



for Lillian J. Gill
Director
Office of Compliance
Center for Devices and Radiological Health

Enclosures